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Breast Cancer

Breast Cancer in African-American Women

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Key Words. Breast cancer · African-American women · Outcome disparities

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the differences in breast cancer incidence and mortality rates between African-American and Caucasian-American women.
2. Describe the patterns of breast cancer risk that are specific to African Americans, including age distribution and hormone receptor expression.
3. Discuss the potential limitations of breast cancer risk assessment for African-American women.

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ABSTRACT

African-American women face a lower risk of being diagnosed with breast cancer as compared to Caucasian-American women, yet they paradoxically face an increased breast cancer mortality hazard. An increased incidence rate for early-onset disease has also been documented. This manuscript review summarizes the socioeconomic, environmental, genetic, and possible primary tumor biologic factors that may explain these disparities. ***The Oncologist*** 2005;10:1-14

INTRODUCTION

Breast cancer incidence is lower in African-American than in Caucasian-American women, yet breast cancer mortality rates are paradoxically higher for African-American women [1, 2]. These poorly understood disparities have been consistently documented in population-based data from the Surveillance, Epidemiology, and End Results (SEER) program since its inception in 1976 [1, 2]. Another notable feature regarding ethnicity-related variation in the epidemiology of breast cancer is that African-American women face a greater risk for being diagnosed with early-onset disease. This review summarizes the information available on the epidemiology of breast cancer in African-American women, as well the possible socioeconomic, genetic, and primary tumor biologic factors that account for these variations.

CLINICAL EPIDEMIOLOGY

As shown in Figure 1, breast cancer incidence is lower for African-American than for Caucasian-American women, yet

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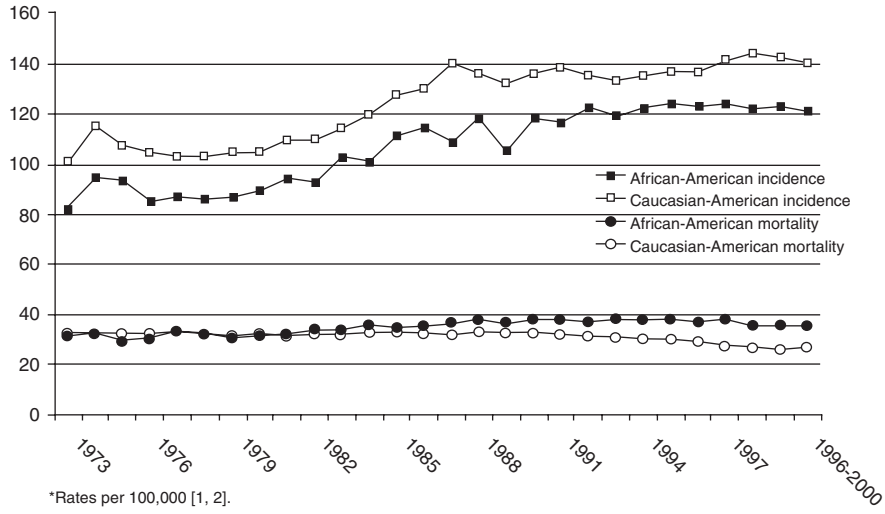

Figure 1. Breast cancer incidence and mortality in African and Caucasian Americans.

the SEER program population-based data have documented higher breast cancer mortality rates among the African-American community. The higher mortality rates are at least partially explained by the more advanced stage distribution that is seen among African-American breast cancer patients, and these disparities are shown in Table 1 [1, 2].

The prevalence and strength of the established breast cancer risk factors among African-American women are not well documented, but some differences in the significance of various factors have been reported [3, 4] in analyses of the Contraceptives and Steroid Hormone (CASH) study. Mayberry and Stoddard-Wright [3] analyzed standard familial and gynecologic risk factors among breast cancer cases (3,934 Caucasian Americans, 490 African Americans) and controls (3,901 Caucasian Americans, 485 African Americans) from the CASH study and found that age at first live birth, parity, and surgical menopause had similar associations with breast cancer risk, but family history and age at menarche behaved differently as risk factors. For African Americans, first-degree and second-degree family history of breast cancer had comparable strengths as risk factors (odds ratios, 1.61 and 1.71, respectively), whereas the association in Caucasian Americans was notably stronger in relation to the pattern of family history (odds ratio, 2.16 for first-degree relatives, and 1.44 for second-degree relatives). Relatively younger ages at menarche have also been reported for African-American women [5], but the impact of this finding on breast cancer incidence has not been defined.

An intriguing pattern of breast cancer in African-American women is seen in the age-incidence curves for the disease, as demonstrated in Figure 2 [1, 2]. Although breast cancer risk clearly increases as a function of age, African-American women under the age of 45 years have a greater incidence of breast cancer than Caucasian-American women in this young age range. These rates equalize during the fifth decade of life, and for women over the age of 50 years, incidence rates for Caucasian Americans surpass those for African Americans, resulting in an overall higher lifetime risk for the Caucasian Americans. Although the absolute values of these population-based incidence rates may not appear very large in magnitude, this ethnicity-related variation in age distribution is far more striking in clinical practice, where 20% of Caucasian-American breast cancer patients are younger than 50 years of age, compared with 30%–40% of African-American breast cancer patients [6].

It has been reported that the crossover in breast cancer age incidence between African-American and Caucasian-American women is a relatively recent phenomenon that evolved over the 1960s [7]. A sudden shift in age distribution is difficult to explain, making the accuracy of this observation dubious. The SEER program is the most well-established and comprehensive registry of population-based cancer data in the U.S., and case ascertainment for SEER began in 1974. One could easily speculate that research regarding the cancer burden among African Americans was inadequately documented during the first half of the twentieth century.

A plausible and interesting explanation for the younger age distribution of African-American breast cancer patients has been proposed by Pathak et al. [8]. Those investigators correlated the short-term increase in breast cancer risk that occurs in the postpartum period with premenopausal breast cancer risk. They hypothesized that the higher prevalence of early childbearing that is observed among African-American compared with Caucasian-American women thereby accounts for the higher incidence of early-onset breast cancer. Palmer et al. [9] reported supporting data for this concept in an analysis of The Black Women's Health Study. Those investigators demonstrated a dual effect of pregnancy on breast cancer risk: multiparity increased breast cancer risk prior to the age of 45 years but was protective against breast cancer risk after age 45.

Postmenopausal obesity is an established risk factor for breast cancer [10] because of the higher circulating estrogen

Table 1. Results of selected studies comparing breast cancer in African-American and Caucasian-American women

Study	Dataset	Feature		Caucasian-Americans	African-Americans
Li et al. [82]	SEER	*n*		97,999	10,560
		Stage (%)	I	50.4	35.4
			III/IV	11.3	18.9
		High-grade tumors (%)		32.1	43.2
		Tumor ≥5 cm (%)		8.0	15.0
		Node-negative (%)		53.9	42.6
		ER-negative (%)		22.0	39.2
		PR-negative (%)		31.7	46.6
		Mortality hazard (95% CI)		1.0 (ref)	1.5 (1.4–1.6)
Li et al. [81]	SEER	*n*		75,978	6,915
	Age ≥50 years	Stage (%)	I	53.2	39.1
			III/IV	11.1	19.1
		High-grade tumors (%)		29.0	37.6
		Tumor ≥5 cm (%)		7.4	14.1
		Node-negative (%)		54.3	43.2
		ER-negative (%)		15.2	24.1
		PR-negative (%)		23.8	30.4
Newman et al. [36]	Detroit SEER	*n*		1,378	507
	Age <40 years	Localized stage (%)		52.1	42.4
		Median tumor size (cm)		2.6	3.4
		Node-negative (%)		45.7	33.3
		ER-negative (%)		44.4	61.9
		PR-negative (%)		48.8	59.7
		Mean survival (months)		50	45
Shavers et al. [37]	SEER	*n*		2,638	724
	Age <35 years	Stage (%)	I	26.7	16.4
			III/IV	12.3	16.7
		High-grade tumors (%)		43.3	54.8
		Median tumor size (cm)		2.5	2.8
		Node-negative (%)		44.6	36.5
		ER-negative (%)		33.1	34.4
		PR-negative (%)		35.4	35.6
		Mastectomy (%)		53.2	53.7
		5-year disease-specific survival		76.5	66.6
		Mortality hazard (95% CI)		1.0 (ref)	1.3 (1.0–1.6)
Elledge et al. [80]	San Antonio database	*n*		4,885	1,016
		Age >50 yrs (%)		76.1	62.6
		P53-positive (%)		50.9	54.9
		Tumor ≥5 cm (%)		10.9	27.7
		Node-negative (%)		57.9	48.8
		ER-negative (%)		22.1	37.9
		PR-negative (%)		44.0	59.2
		HER2/*neu*-positive (%)		16.1	13.8
		5-year overall survival (%)		75	65
		Median survival (months)		166	117
Boyer-Chammard et al. [103]	Southern California	*n*		10,937	185
		Localized disease (%)		61.4	50.8
		Median age (years)		64	52
		Mortality hazard		1.0 (ref)	2.32 (1.76–3.07)
Clegg et al. [52]	SEER				
	Age ≥50 years	2-year mammography screening rates (%)		70	67

Abbreviations: CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor

levels that result from fatty tissue metabolism of adrenal gland steroids in the absence of ovarian function. Flegal et al. [11] analyzed the Third National Health and Nutrition Examination Survey (NHANES III) and found that more than half the African-American women over the age of 40 years were obese (body mass index ≥30), and more than

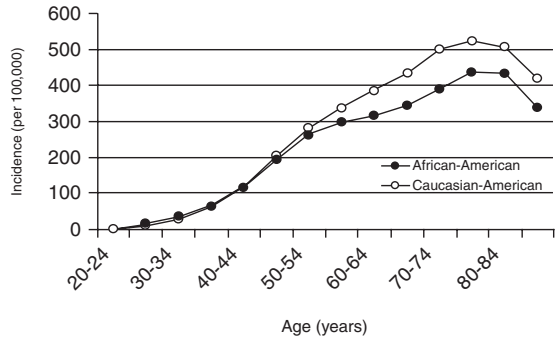

Figure 2. Age-incidence curves for breast cancer in African-American and Caucasian-American women.

80% were overweight (body mass index ≥25). However, as noted previously, breast cancer incidence rates are significantly lower for African-American women in the postmenopausal age range. The extent to which dietary fat contributes to breast cancer incidence among African-American women is unclear at present. Other NHANES findings have implicated physical inactivity and inadequate intake of micronutrients, as well as other dietary components, as factors contributing to pre- and postmenopausal breast cancer risk among African-American women [12].

Breast cancer risk is a function of both environmental/lifestyle exposures and genetic factors. It is therefore appropriate to compare patterns of the disease among African Americans with data regarding the epidemiology of breast cancer among native African women. Unfortunately, there is a paucity of population-based data regarding breast cancer incidence and mortality in Africa, a large continent comprised of many diverse nations. Nonetheless, available data reveal several provocative parallels between African-American and native African breast cancer patients. Overall, breast cancer is a relatively unusual malignancy in African countries. Several investigators have documented a younger age distribution and a greater prevalence of high-grade, estrogen-receptor-negative disease among breast cancer patients in the Ghanaian and Nigerian populations of western Africa [13–16], similar to the patterns of breast cancer reported among African-American women. Western African populations served as the source for most of the slave trade to colonial North America, and therefore share a common ancestry with present-generation African Americans. These parallels suggest the possible contribution of founder effects.

Molecular and Genetic Epidemiology

Early studies of BRCA mutations suggested that they were relatively rare among African-American women [17]. Since that time, however, several BRCA-related breast cancers in African-American women have been identified [18–22], and these studies are reviewed comprehensively by Olopade et al. [23]. Germline mutations in the BRCA genes that are specifically associated with high-risk (but unrelated) African-American kindreds have also been identified [18, 21, 23], and it is possible that additional African-associated founder mutations in other breast cancer susceptibility genes will be identified in the future. While population-based studies regarding the prevalence of mutations in breast cancer susceptibility genes are under way, no definitive data are available at present. Several reports have demonstrated that African-American women tend to underutilize genetic counseling services [24–26], and Matthews et al. [24] have underscored the importance of tailored outreach/educational strategies in order to improve the participation rates of African-American women in genetic counseling programs. Currently available data on genetic predisposition to breast cancer among African Americans are inadequate for drawing any conclusions regarding whether ethnicity-specific guidelines are warranted for identifying members of mutation-carrying kindreds. African-American families appearing to be at high risk for harboring a BRCA mutation require complete gene sequencing.

Several investigators have confirmed an association between circulating levels of sex hormones and breast cancer risk [27–31]. Ethnicity-related variation in levels of endogenous hormones [32, 33] has also been reported, and this issue warrants further study. Bone density is one surrogate marker of estrogen levels, and it has been associated with a higher breast cancer risk. African-American women tend to be less susceptible to osteoporosis, and greater radial bone density has been correlated with breast cancer risk among African-American women by Nelson et al. [34]. Poola et al. [35] have shown that expression of the beta isoform in the estrogen receptor (which may be protective against abnormal proliferative changes in mammary epithelial tissue) may be disproportionately low in African-American women. Studies thus far provide opportunities for speculation, but they fail to offer a clear picture of how hormone levels might account for the unique epidemiology of breast cancer in African-American women.

As shown in Table 1, the tumors of African-American breast cancer patients are significantly more likely to be hormone-receptor negative, aneuploid, and node positive. These patterns persist even after controlling for stage and age, as demonstrated in studies by Newman et al. [36] and Shavers et al. [37]. Furthermore, as biomedical research and genotyping tools develop further, contemporary studies are identifying other provocative characteristics that appear to be specific to African-American breast cancer patients. The results of several such studies, examining variations in cytochrome P450

polymorphisms, estrogen receptor β, p53, and other markers, are shown in Table 2. These latter observations require validation and expansion before their clinical relevance can be appropriately defined.

Table 2. Selected studies of primary tumor biology in African-American breast cancer patients, based on contemporary biomedical and molecular epidemiologic analyses

Study	Sample size	Technology/Analysis	Findings
Elledge et al. [80]	4,885 Caucasian-American breast cancer patients 1,016 African-American breast cancer patients 777 Hispanic-American breast cancer patients	Immunohistochemistry for ER/PR, HER2/*neu*, p53; flow cytometry for S-phase fraction and DNA ploidy status	Tumors of African-American women more likely to be hormone receptor negative, with higher S-phase fraction
Shiao et al. [110]	47 Caucasian-American breast cancer patients 45 African-American breast cancer patients	PCR single-strand conformational polymorphism analysis and DNA sequencing	Similar rates of somatic p53 mutations, but specific alterations varied between African-American and Caucasian-American patients
Guillemette et al. [111]	200 African-American breast cancer patients 200 African-American controls	Reverse transcriptase PCR analysis	African-American-specific polymorphisms in UG1A1, a steroid-metabolizing gene
Poola et al. [35]	24 African-American breast cancer patients	Reverse transcriptase PCR to analyze estrogen receptor isoforms	Lower expression of estrogen receptor-β and higher expression of estrogen receptor-α exon 5 Δ isoforms
Mehrotra et al. [112]	44 Caucasian-American breast cancer patients 67 African-American breast cancer patients	Methylation-specific PCR to analyze HIN-2; Twist; cyclin D-2; RASSFIA; in situ hybridization PCR to analyze HIN-1 mRNA	Higher frequency of multiple gene methylation in young African-American women with estrogen receptor-negative and progesterone receptor-negative tumors
Chen et al. [113]	149 African-American women 67 Asian-American women 226 Caucasian-American women	Computer-assisted measurements of mammographic density in Asian-American, African-American, and Caucasian-American women	Ethnic differences in breast density correlated with ethnic variation in risk require adjustment for age, body mass index, and reproductive factors; measurements of absolute density are more meaningful than proportion of dense tissue.
Porter et al. [114]	124 African-American breast cancer patients 397 Caucasian-American breast cancer patients	Immunohistochemistry for ER/PR, HER2/*neu*, Ki67, p53, cyclin E, cyclin D1, p27, p16, pRb, and p21	Tumors of African-American women more likely to be higher grade, and associated with higher mitotic index, ER/PR negativity, overexpression of cyclin E, p16, and p53, and low expression of cyclin D1 compared with tumors of Caucasian-American women
Millikan et al. [115]	760 African-American breast cancer patients 1,265 Caucasian-American breast cancer patients	Genotyping for manganese superoxide dismutase Ala-9Val polymorphism	Similar predictive value of polymorphism among African-American and Caucasian-American breast cancer patients; polymorphism only associated with breast cancer in cases with smoking history, chest wall XRT, and occupational radiation exposure
Li et al. [116]	271 African-American breast cancer patients; 285 controls 417 Caucasian-American breast cancer patients; 417 controls	Genotyping for cytochrome P450 1A1 (CYP1A1) polymorphisms	Particular CYP 1A1 polymorphisms associated with higher breast cancer risk among smokers
Jones [117]	177 Caucasian-American breast cancer patients 145 African-American breast cancer patients	Immunohistochemistry for c-met, p53	Greater prevalence of p53 alterations among African-American women

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; PCR = polymerase chain reaction; XRT = radiation therapy

Risk Assessment and Chemoprevention

Risk assessment research has assumed an increased level of importance in light of the confirmed efficacy of tamoxifen [38], prophylactic mastectomy [39], and prophylactic oophorectomy [40] in reducing breast cancer incidence among high-risk women. The potential adverse events associated with all these risk-reducing strategies mandate the accurate identification of high-risk women for whom accepting the intervention-related hazards would be worthwhile.

Use of the selective estrogen-receptor modulator tamoxifen for chemoprevention is particularly relevant to a discussion of African Americans and breast cancer. Tamoxifen only reduces the risk of estrogen receptor-positive tumors, and African-American women have a relatively lower risk for being diagnosed with these favorable lesions. Furthermore, tamoxifen can cause thromboembolic phenomena, and morbidity from deep vein thrombosis/pulmonary emboli is relatively high among African-American women. On the other hand, tamoxifen-associated adverse events are uncommon among young women, and premenopausal African-American women face a higher risk for developing breast cancer. Unfortunately, only 1.7% of the National Surgical Adjuvant Breast Project (NSABP)-P01 participants were African American [38], and we therefore have no data on efficacy of tamoxifen for pure chemoprevention in this population subset.

Freedman et al. [41] analyzed breast cancer risk factor data compiled by the year 2000 National Health Interview Survey Cancer Control Module in conjunction with the Gail tamoxifen benefit/risk index [42] to estimate the proportion of adult women in the U.S. who could benefit from tamoxifen therapy. For Caucasian-American women, 15.5% would be eligible on the basis of risk estimates alone and 4.9% would have a favorable benefit/risk index. For African-American women, these rates were notably smaller in magnitude: 5.7% estimated to be risk eligible and 0.6% estimated to have a favorable benefit/risk index. The relatively low estimates for African-American women are disappointing in light of their known disproportionately elevated risk for breast cancer mortality. It should be noted, however, that the benefit/risk analysis accounts for a presumed greater risk for thromboembolism and stroke among African-American women (based on extrapolations from mortality data), but ethnicity-related differences in breast cancer mortality are not weighted into the index.

The incomplete understanding of risk factor exposures in African-American women has resulted in doubts regarding our ability to accurately predict breast cancer risk in this population subset via the established tools utilized for Caucasian-American women. The Gail breast cancer risk assessment model [43] allows for estimation of individualized likelihood of developing breast cancer. This model is a logistic regression equation based on risk factor data from participants of the Breast Cancer Detection and Demonstration Project, a mammography screening program conducted by the American Cancer Society during the 1970s. Very few African-American women participated in this program, and the model was, therefore, limited to risk factor exposure data from a case-control subset of the Caucasian participants, and in its original formulation it was appropriately labeled as a model to predict breast cancer risk in Caucasian-American women receiving annual mammographic screening. Risk estimates computed by this model are the primary means of determining eligibility for the NSABP chemoprevention trials, and so the model has been modified to adjust for risk calculations in African-American women as well.

The Gail model quantifies breast cancer risk by multiplying the relative risks for four different factors by the woman's age-specific baseline hazard for developing breast cancer. The model risk factors are age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and number of breast biopsies. The age-specific baseline risk represents the absolute likelihood that a woman will develop breast cancer in the absence of increased risk conferred by the four model risk factors; this baseline is derived from SEER program age- and ethnicity-specific breast cancer incidence rates. The SEER program provides breast cancer incidence for the general population of women and a composite of various risk factor expressions. An approximation of the true baseline risk is extrapolated from these composite-risk incidence rates by subtracting the amount of disease that is estimated to have resulted from risk conferred by the four model risk factors (population attributable risk). Population attributable risk estimates are typically calculated from known data on risk factor prevalence rates.

The validity of the Gail model in accurately identifying groups of high-risk patients was demonstrated in three different populations of Caucasian-American women [44–47]. Recently, the model was evaluated in African-American women based on case-control data from the Women's Contraceptive and Reproductive Experiences study. This analysis suggested that the model tends to underestimate risk for African-American women and generated questions regarding accuracy of the baseline risk estimate component of the model, especially for the subset of young African-American women [48, 49]. Utilization of a revised model with adjusted baseline risk estimates has been proposed.

Early Detection and Screening

The relatively more advanced stage distribution of breast cancer motivates the concern that African-American women receive suboptimal breast cancer surveillance. Widespread

adoption of annual mammography screening practices since the 1970s among American women over the age of 40 years is credited for the recent improvements observed in population-based breast cancer outcome, as a direct consequence of increasing the proportion of screen-detected early-stage tumors [50]. SEER data reveal that between 1983 and 1998, the proportions of in situ and stage I disease doubled for the entire population [1]. As noted previously, however, African-American women continue to present with greater proportions of advanced-stage disease, despite recent data indicating increases in mammography utilization among African-American women that are comparable with utilization rates among Caucasian-American women, approaching 70% [51]. Hence, the impact of screening patterns and follow-up in African-American women is incompletely understood.

The National Health Interview Survey (NHIS) utilizes specially trained U.S. Census Bureau personnel to collect health status and health care information on representative segments of the American population via personal household interviews conducted continuously since 1975. NHIS data reveal significant increases in utilization of mammography screening for both African Americans and Caucasian Americans since 1987. For women over 40 years of age, approximately one-quarter of both groups reported having had a mammogram within the past 2 years in 1987. In 2000, these rates increased to 71.4% for Caucasian Americans and 67.8% for African-American women. Interestingly, the disparity in mammography utilization is larger for women aged 40–49 years, where the rates are 67.1% for Caucasian and 60.9% for African Americans [51–53].

The younger age distribution for breast cancer among African-American women leads to concerns regarding the efficacy of screening mammography, an imaging modality with limited accuracy in young women. This issue is not addressed in any of the original mammography screening trials because few African-American women were included in those phase III studies [54]. The international trials, by definition, would not have been expected to sample African-American women, and the Health Initiatives Program of New York screening trial included fewer than 6% African-American participants. The paucity of data regarding surveillance mammography in African-Americans is reviewed by Royak-Schaler and Rose [55]. Jones et al. [56] reported that history of mammographic screening accounted for less than 10% of the higher risk for advanced-stage disease observed in a population-based study of breast cancer in African-American compared with Caucasian-American women from Connecticut. In contrast, McCarthy et al. [57] linked Medicare records on mammography claims with SEER data and found that history of mammography use accounted for 30% of the stage distribution disparity between older-aged African-American and Caucasian-American women. Patterson et al. [58] reported similar mammographic appearance for breast cancers detected in African-American compared with Caucasian-American women.

Effect of Socioeconomic Status (SES)

In 1989, Freeman and Wasfie documented the powerful effects of African-American ethnicity combined with poverty on breast cancer outcome based on data from the Harlem Hospital Center [59]. That study reported a 39% 5-year survival rate for 512 surgically treated breast cancer patients between 1964 and 1986. Ninety-four percent of those patients were African American and only 6% presented with stage I disease, suggesting that few women in that system were undergoing mammographic screening for breast cancer. The Breast Examination Center of Harlem was established to address this health care deficit, and recently published findings [60] from that center demonstrate dramatic improvements in breast cancer stage distribution for the Harlem population. Between 1995 and 2000, nearly half the breast cancers detected were stage 0 or I disease.

Successful outreach and surveillance programs such as these suggest that ethnicity-related disparities in breast cancer survival can be reduced substantially by optimizing early detection with mammographic screening. However, national data have revealed a narrowing in the magnitude of difference for mammography utilization rates for African-American compared with Caucasian-American women, and yet differences in stage distribution persist. It might, therefore, be inferred that outcome disparities will not be eliminated entirely by intensive screening efforts alone.

Socioeconomic factors probably account for a substantial proportion of breast cancer outcome disparities. As shown in Figure 3, poverty rates, likelihood of lacking medical insurance, and likelihood of relying on public insurance such as Medicaid are twice as high for African Americans

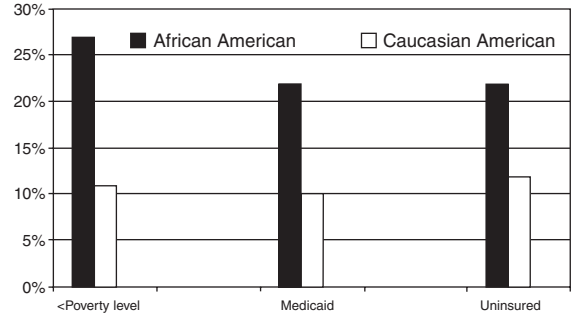

Figure 3. Proportions of African Americans compared with Caucasian Americans living below the poverty level, covered by Medicaid insurance, or completely uninsured [102].

compared with Caucasian Americans. These economic barriers to health care access certainly contribute to delays in breast cancer diagnosis and treatment, ultimately resulting in higher mortality rates.

Several studies have attempted to account for SES in evaluating ethnicity-related variation in breast cancer outcome. Findings from fourteen studies [61–74] published over the past 20 years were analyzed in a meta-analysis reported by Newman et al. [75]. Several patterns were apparent on careful scrutiny of these studies. First, socioeconomic disadvantages are more prevalent among African-American compared with Caucasian-American patients, as expected. Secondly, crude survival analyses demonstrate worse outcomes for the African-American breast cancer patients, which correlates with national population-based data from the SEER program. A third and final pattern is that adjustments to the survival analyses based on SES generally result in diminution or complete elimination of any statistically significant association with ethnicity. A necessary corollary to the adjusted survival comparisons is a reduction in the statistical power to evaluate ethnicity and SES, since the resulting comparison involves a relatively smaller subset of affluent African-American breast cancer patients and a relatively larger subset of affluent Caucasian-American breast cancer patients. The pooled data yielded a more robust sample size, with more than 10,000 African-American and 40,000 Caucasian-American breast cancer patients contributing to the analysis. After adjusting for SES, stage, and age at diagnosis, a 22% higher mortality risk was seen among the African-American patients (mortality odds ratio, 1.22; 95% confidence interval: 1.13-1.30). The individual studies included in this meta-analysis evaluated other markers of tumor biology to varying degrees. Some studies included tumor grade, some included hormone receptor status, and others included histology in their adjusted, proportional hazards survival analyses. The summary data from the pooled analysis are shown in Figure 4.

Bradley et al. [76] published a recent report that underscores the complexities of SES and breast cancer survival analyses. Those investigators utilized Medicaid and census tract data linked to the Metropolitan Detroit SEER registry. African-American background was a predictor of worse outcome on univariate analysis; however, in the multivariate analysis that adjusted for residence in a high-poverty neighborhood (at least 5% of households below the poverty level), Medicaid coverage, stage, age, marital status, treatment, and disease stage retained the strongest significance levels independently. Notably, more than half the entire study population was categorized as residing in a low-income neighborhood, and only 19% of the study population was African American. The sample size of African-American breast cancer patients who were coded as not being poor was probably very small, and this study was therefore left with neither ethnicity nor SES retaining statistical significance. The authors nonetheless concluded that SES was probably the major determinant of poor outcome by leading to advanced stage at diagnosis.

As discussed in the meta-analysis, measures of SES are inconsistent and poorly validated. Furthermore, the prognostic value of SES is easily confounded by diet, lifestyle, and cultural factors, all of which may have ethnicity-based variations. Barriers to health care access secondary to poverty clearly exert a negative influence on breast cancer outcome. Quantifying the independent effects of SES, ethnicity, hereditary factors, and lifestyle/environmental exposures on breast tumor biology is therefore a formidable challenge.

Treatment Effects

Ethnicity-related variation in breast cancer treatment could influence outcome as a consequence of either A) inherent resistance to therapy related to primary disease factors or B) inequalities in delivery of care. There is heterogeneity in breast tumor biology as well as in health care environments, and the individual breast cancer patient might therefore be impacted by either, both, or neither of these factors.

Locoregional recurrence rates tend to be higher in younger breast cancer patients treated by lumpectomy. The younger age distribution of African-American breast cancer patients therefore warrants a closer look at outcome following breast conservation therapy (BCT). Several studies (Table 3) have, therefore, evaluated BCT in African-American and Caucasian-American breast cancer patients. As reviewed by Newman et al. [77], overall BCT utilization rates are relatively low for both patient populations, and

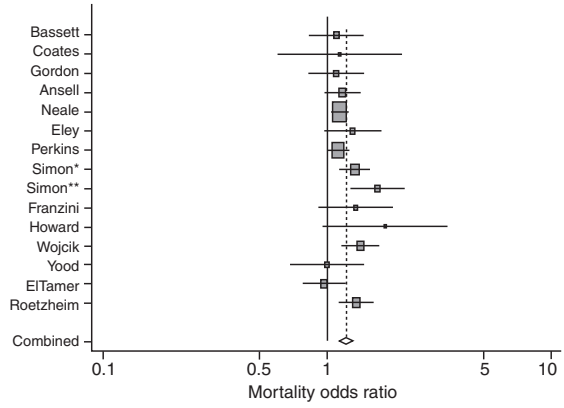

Figure 4. Meta-analysis of studies comparing outcome from breast cancer in African-American (n = 10,001) and Caucasian-American (n = 42,473) patients, after adjusting for age, stage, and SES. Mortality odds ratio 1.22; 95% confidence interval 1.13-1.30. *Patients <50 years of age. **Patients ≥50 years of age [75].

Table 3. Selected studies of breast conservation therapy in African-American women

	n of patients				
Study	**African American**	**Caucasian**	**Study criteria**	**Median follow-up**	**Findings**
Burri et al. [104]	72	29	All BCT cases; mostly indigent population	Estimated 5 years	Local control for African-American patients 95.2% at 5 years; 87.9% at 10 years; Disease-free survival rate for African-American patients 84.6% at 5 years; 65.3% at 10 years.
Connor et al. [105]	71	204	Stage I/II; all treated with BCT	53 months	Trend for higher local recurrence rate in African Americans (n.s.)
Nicolaou et al. [106]	41	301	Stage IIA/B; node positive; all treated with BCT	73 months	Higher regional relapse rate among African Americans (19% versus 1%; $p < 0.0001$)
Velanovich et al. [107]	416	834	Stages I-IV; treatment variable	NA	Similar rates of BCT among African-American and Caucasian-American patients (54.5% versus 57.2%)
Newman et al. [78]	211	NA	T1/T2 tumors; treatment variable	68 months	BCT rate 19.9% Similar local recurrence and survival rates in BCT and mastectomy patients (9.8% versus 8.9%)
Arnold et al. [108]	107	131	All treated in an urban teaching hospital	NA	BCT rate 36% for African-Americans; 41% for Caucasian-American patients
Muss et al. [109]	160	145	Stage II; node positive; treatment variable	NA	Lower BCT rates among African-American than among Caucasian-Americans patients (22% versus 40%; $p = 0.004$)
Pierce et al. [79]	75	615	Stage I/II; all treated with BCT	56 months	Similar local recurrence rates for African-American and Caucasian-Americans patients (5% versus 6%); higher regional relapse rates for African-American patients (16% versus 4%; $p = 0.001$)

Abbreviation: n.s. = not significant

although some data indicate a higher risk of local recurrence for African-American women, this may be related to underlying tumor biology, as the risk of local recurrence is greater following mastectomy as well [78]. Some interesting patterns of locoregional and distant failure following BCT were reported by Pierce et al. [79] in a study of BCT in 75 African-American and 615 Caucasian-American breast cancer patients. Local-only recurrence was similarly low for both subsets of patients (5% and 6%, respectively), but the risks of regional failure (especially in the supraclavicular nodal basin) and distant metastases were significantly higher for the African-American patients.

As noted previously, African-American breast cancer patients are more likely to have estrogen receptor-negative disease [36, 37, 80–82]. This variation clearly influences cancer management, as endocrine therapy is contraindicated and replaced by chemotherapy as the only option for adjuvant systemic treatment for these estrogen receptor-negative tumors. For African-American patients with estrogen receptor-positive tumors, however, hormonal therapy with tamoxifen appears to have equivalent efficacy to when delivered to Caucasian-American breast cancer patients, as demonstrated by McCaskill-Stevens et al. [83] in a pooled analysis of NSABP adjuvant therapy studies. Nonetheless, population-based data on comorbidities raise some interesting questions with regard to selection of endocrine therapy. As noted previously, thromboembolism is relatively more prevalent among African Americans and is also a known potential complication of tamoxifen therapy. Aromatase inhibitors have a lower risk of exacerbating thromboembolic problems but pose a risk of accelerated osteoporosis [84]. African-American women tend to have a lower risk of osteoporotic bones than Caucasian-American women. One might, therefore, postulate that aromatase inhibitors would be the preferred hormonal therapy for postmenopausal African-American women diagnosed with estrogen receptor-positive breast cancer. Unfortunately, there are no published data on efficacy and side effects of aromatase inhibitors in African-American women.

Chemosensitivity of breast cancer in African Americans has been studied indirectly. Growing work in the area of pharmacogenetics is resulting in the identification of various

polymorphisms in proteins that are involved with metabolism of cancer-treating therapies. Polymorphisms in cytochrome P450/CYP enzymes are known to have variable prevalence rates among different ethnically defined subsets of the population [85, 86] and could potentially alter chemotherapy effectiveness. Review of the MD Anderson locally advanced breast cancer database, however, revealed similar clinical and pathologic response rates to induction chemotherapy for African-American and Caucasian-American breast cancer patients [87].

A provocative study, reported by Hershman et al. [88], demonstrated that African-American breast cancer patients were more likely to experience delays in completion of adjuvant chemotherapy regimens related to neutropenia, and that this prolongation of treatment may correlate with a lower overall dose intensity. Interestingly, the clinical relevance of ethnicity-related neutropenia is poorly understood, as baseline neutrophil counts were lower among the African-American patients, and this hematologic pattern has been noted among the general population as well. The potential confounding effect of obesity rates among African-American breast cancer patients and its impact on chemotherapy dosing also requires further study.

Unfortunately, disparities in delivery of treatment to African-American breast cancer patients have also been reported [89], raising the concern that discriminatory practices in the health care system may also contribute to outcome disparities. These disparities may be unintentional and related to miscommunication between patient and health care provider or they may be related to socioeconomic issues. Chu et al. [90] reported that the magnitude of difference in breast cancer outcome between African-American and Caucasian-American patients was minimized among women age 65 or older, and the authors interpreted their findings as implying that more effective breast cancer treatment was delivered to women who were more likely to have health care coverage by virtue of being age eligible for Medicare benefits. Breen et al. [89] found evidence of unequal breast cancer management in a subset analysis conducted on participants of the Black/White Cancer Survival Study, where 21% of African-American patients failed to receive the minimum expected standard of care (as defined by National Cancer Institute consensus statements), compared with 15% of Caucasian-American patients.

Standardization of care through the clinical trials mechanism would be expected to abolish the influence of ethnicity-related treatment and/or socioeconomic disparities on breast cancer outcome, thereby providing a "pure" assessment of ethnicity-related survival. Roach et al. [91] examined breast cancer survival among African-American and Caucasian-American participants of a Cancer and Leukemia Group B phase III study of node-positive disease and found a worse outcome for the African Americans in a univariate analysis. The investigators were able to eliminate the statistical significance of this association by performing a multivariate logistic regression analysis that included age, hormone-receptor expression, number of metastatic nodes, and chemotherapy dose. This latter analysis was clearly affected by progressive loss of statistical power related to small subset sample sizes.

Subset analyses of NSABP trials have yielded inconsistent results regarding the influence of ethnic background on outcome. An early analysis of outcome predictors for the NSABP B-06 trial revealed worse survival for African-American participants [92]. In contrast, more recent reviews of the NSABP protocols reported by Dignam [93, 94] revealed that, after accounting for other primary tumor features, African-American ethnicity was generally not an independent predictor of worse disease-free outcome. Overall mortality rates, however, were significantly higher for African Americans, suggesting that comorbidities may be exerting an effect.

Albain et al. [95] conducted one of the most recent and powerful studies presented to date on the issue of ethnicity-related breast cancer outcome within the context of the clinical trials setting. The Southwest Oncology Group pooled the data on all breast cancer patients (nearly 7,000 cases) participating in five prospective, randomized, adjuvant therapy clinical trials conducted between 1975 and 1995. Albain et al. analyzed survival for these studies (consisting of approximately 10% African-American patients) after adjusting for SES, age, and disease stage. They found that African-American ethnicity was a statistically significant and independent predictor of mortality risk in the multivariate survival analyses of both pre- and postmenopausal breast cancer patients. Hazard ratios for mortality in the overall survival analysis were 1.41 (95% confidence interval, 1.10–1.82) for premenopausal African-American women and 1.49 (95% confidence interval, 1.28–1.73) for postmenopausal African-American women. Similar statistically significant outcome disadvantages were reported for disease-free survival.

Future Directions

As biomedical technology and techniques of molecular epidemiology continue to mature, we are likely to gain improved insight regarding modifiable versus fixed determinants of breast cancer risk as well as treatment response. However, it will be incumbent upon the oncology research community to design studies that account for ethnic ancestry to the greatest extent possible, so that ethnicity-related variations can be defined. The health care provider

community must assume responsibility for implementing outreach programs that optimize African-American participation in genetic counseling programs, breast cancer screening programs, and treatment, as well as chemoprevention clinical trials. These efforts will strengthen the likelihood of successful research endeavors. The importance of survivor advocates, social networks, and church-based support groups appears to be quite valuable in achieving the outreach goals [96–100]. In particular, cancer care providers should be aware of the Sisters Network, Inc., a national African-American survivor advocate organization that has provided breast health awareness information and clinical trials support to thousands of women in the African-American community since its inception in 1994 [101]. Information regarding the support services and resources offered by this organization is available at their website, www.sistersnetwork.com.

Summary

Breast cancer pathogenesis and epidemiology are complex and influenced by the myriad of environmental and lifestyle factors that impact on lifetime hormone exposures. The genetic, socioeconomic, and cultural features associated with ethnic background complicate the picture further. For African-American women these various elements converge to yield the paradoxical patterns of a relatively lower breast cancer incidence, higher mortality rate, and younger age distribution. Expanded breast cancer screening programs and attention to assuring equality in delivery of care should result in some degree of improved outcome. It is also essential to ensure increased accrual of African Americans into chemoprevention as well as treatment trials. As microarray technology to evaluate the genetic composition of tumors becomes more widely available, many of the questions regarding ethnicity-associated variation in primary cancer biology will be clarified.

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